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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,179	UEMATSU ET AL.	
	Examiner	Art Unit	
	STEPHANIE K. MUMMERT	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10-16* is/are pending in the application.

4a) Of the above claim(s) *10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/20/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on March 3, 2008 is acknowledged and has been entered. Claims 1, 9 and 14 have been amended. Claim 8 has been canceled. Claims 15-16 have been added. Claims 1-7 and 14-16 are pending. Claims 10-13 are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-7 and 14-16 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL.

New Grounds of Rejection necessitated by Amendment

Information Disclosure Statement

The information disclosure statement (IDS) submitted on February 20, 2008 was filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

However, it is noted that the Notice of Rejection is in Japanese and a translation was not provided. A statement regarding the specific rejections included in the Notice is included in the statement accompanying the IDS. However, the Notice has only been considered insofar as the inclusion of references specifically cited in the IDS.

Priority

Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-2, 9 and 15-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Uematsu et al. (Nucleic Acids Research Supplement No. 2, 2002, p. 211-212, public availability date of August 9, 2003, see printout from Pubmed; 'Uematsu 2002' herein) as evidenced by Uematsu et al. (2001, Nucleic Acids Research, vol. 29, no. 16, e84, p. 1-6; 'Uematsu 2001' herein). Uematsu teaches real-time detection of PCR products using "module shuffling" TaqMan probes (Abstract).

With regard to claim 1, Uematsu 2002 teaches a method for expressed gene analysis comprising:

subjecting a gene to be analyzed to nucleic acid amplification using a forward primer specifically hybridizing to the gene to be analyzed, a primer for introduction comprising a first base sequence

closer to the 5' end of the primer than a third base sequence comprising a sequence specifically hybridizing to a target gene, the target gene having a base sequence, and comprising a second base sequence closer to the 5' end of the primer than the first base sequence (Figure 1, where the reverse transcription primer comprises a target specific portion (black box), a probe specific portion (diagonal lined box), and a primer specific portion (vertical lined box)), a probe comprising a base sequence identical or complementary to the first base sequence and labeled at one end with a fluorophore and at another end with a quencher, reverse transcriptase, RNA polymerase, and ribonuclease H and/or exonuclease (Figure 1, where the probe is labeled at one end with a fluorophore and the other end with a quencher), wherein two or more target genes are simultaneously detected in a single reaction vessel using two or more types of probes (Figure 1, where two targets are simultaneously detected), and wherein each of the two or more types of probes comprises several module sequences of 3 or 4 bases, both of the terminal bases of each module sequence are identical to each other and each probe is constituted by rearranging the order of the module sequences having identical terminal bases (Figure 1, p. 211, col. 1-2, where the modular sequence probes are described as TaqMan probes with "modular shuffling sequences" (MPT) and are labeled with different fluorophores; and where the length of the modules is evidenced by Uematsu 2001, Abstract, where the modules were 3 or 4 nt in length); digesting the probe bound to the first base sequence by the ribonuclease H or exonuclease at the time of the nucleic acid amplification (Figure 1, where the modular probe bound is digested); and detecting fluorescence emitted by the released fluorophore, thereby assaying the amount of the product of the nucleic acid amplification, wherein the gene to be analyzed is prepared by the introduction of the first base sequence being nonspecific to the base sequence of the target gene

and the second base sequence comprising a promoter sequence of RNA polymerase, into the target gene so that the second base sequence is bound to a position closer to a 5' end of the gene to be analyzed than the first base sequence (p. 212, where the process of detecting fluorescence is described in detail, see Figures 2a-2b, where fluorescence is measured and detected).

With regard to claim 2, Uematsu 2002 teaches an embodiment of claim 1, wherein the gene to be analyzed is cDNA comprising the first base sequence and the second base sequence introduced therein by the introduction with subjecting the mRNA of the target gene to reverse transcription using the primer for introduction which comprises the first base sequence, which is closer to the 5' end of the primer than the third base sequence comprising a sequence that specifically hybridizes to the target gene and the second base sequence, which is closer to the 5' end of the primer than the first base sequence (Figure 1, where the reverse transcription primer comprises a target specific portion (black box), a probe specific portion (diagonal lined box), and a primer specific portion (vertical lined box)).

With regard to claim 9, Uematsu 2002 teaches an embodiment of claim 1, wherein the melting temperatures (Tm values) of the two or more types of probes are substantially the same (p. 211, col. 1, where the sequences are different but the thermodynamic properties are "almost the same"; as evidenced by Uematsu 2001, Abstract, where the melting temperatures are identical, p. 3-4, where the melting curves are within 2 degrees of each other from 20 to 75oC).

With regard to claim 15, Uematsu 2002 teaches an embodiment of claim 1, wherein the two or more types of probe respectively have fluorophores at one end that emit light at fluorescent wavelengths different from each other (Figure 1, where the probes are labeled with

different reporter fluorophores, R1 and R2; see also p. 212, col. 1, where the labels comprise FAM and VIC).

With regard to claim 16, Uematsu 2002 teaches an embodiment of claim 1, wherein a number of module sequences constituting each probe is in a range of 5 to 8 (p. 211; as evidenced by Uematsu 2001, Figure 1, where the modular primers included at least six different modular sequences within each primer).

Claim Rejections - 35 USC § 103

Claims 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uematsu et al. (Nucleic Acids Research Supplement No. 2, 2002, p. 211-212, public availability date of August 9, 2003, see printout from Pubmed; 'Uematsu 2002' herein) as evidenced by Uematsu et al. (2001, Nucleic Acids Research, vol. 29, no. 16, e84, p. 1-6; 'Uematsu 2001' herein) as applied to claims 1-2, 9 and 15-16 above and further in view of Ovyn et al. (6,101,681; August 2000). Uematsu teaches real-time detection of PCR products using "module shuffling" TaqMan probes (Abstract).

Uematsu 2002 as evidenced by Uematsu 2001 teaches the limitations of claims 1-2, 9, 15 and 16 as recited above. However, Uematsu does not teach the specifics of practicing the method. Ovyn teaches a method for expressed gene analysis comprising NASBA amplification (col. 2, lines 46-49).

With regard to claims 3 and 4, Ovyn teaches an embodiment of claim 1, wherein the nucleic acid amplification is conducted by sequentially repeating the following steps 1) to 3):

1) transcription of the gene to analyzed into RNA with the aid of RNA polymerase (col. 5, lines 46-67, see also Figure 1);

2) reverse transcription of the RNA using the forward primer and the reverse transcriptase or ribonuclease H to synthesize single-stranded cDNA (see Figure 1); and

3) synthesis of the gene to be analyzed from the single-stranded cDNA using the primer for introduction and DNA polymerase (col. 5, lines 46-67 and Figure 1).

With regard to claim 5, Ovyn teaches an embodiment of claim 1, wherein the nucleic acid amplification is conducted at a substantially single temperature (col. 10, lines 15-25, where isothermal amplification of the target RNA was performed at 41°C).

With regard to claim 6, Ovyn teaches an embodiment of claim 5, wherein the single temperature is between 37°C and 55°C (col. 10, lines 15-25, where isothermal amplification of the target RNA was performed at 41°C and wherein 41°C is between 37°C and 55°C).

With regard to claim 7, Ovyn teaches an embodiment of claim 1, wherein the RNA polymerase is T7 RNA polymerase and the second base sequence comprises the T7 promoter sequence (col. 5, lines 46-64, where primer P1 hybridizes to the RNA to prime and initiate 1st strand synthesis and where after second strand synthesis, the complete cDNA includes the T7 promoter site from the P1 primer; see also Figure 1).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have applied the primer format and "universal" detection probe as taught by Uematsu to the method of amplification by NASBA taught by Ovyn. Alternatively, it would have been prima facie obvious to have incorporated the NASBA amplification into the method of detection taught by Uematsu.

Regarding Uematsu 2002, the method is based on a comparative analysis of gene expression using competitive PCR and real-time detection of PCR products. The method incorporates "module shuffling sequences as 'universal TaqMan probes'" and the method "can detect different amounts of expressed genes derived from different sources" (Abstract). Uematsu 2002 also teaches that the "sequences of two TaqMan probes consist of module-shuffling sequences. Their sequences are quite different, but their thermodynamic properties are almost the same" and also notes that the probes "are labeled with different reporter fluorophores at the 5' end and labeled with quencher and Tm enhancer at the 3' end" (p. 211, col. 1). Finally, Uematsu 2002 notes "the MPT method does not require internal standards and MTPs are applicable to any genes as 'universal TaqMan probes'" (p. 212, col. 2).

Regarding the application of this primer format to additional means of amplification, Ovyn teaches a method known as nucleic acid sequence based amplification (NASBA) (col. 2, lines 46-49). Ovyn describes NASBA as "an amplification system that has significant advantages over PCR amplification systems" because it "requires less user participation and fewer manipulations and steps" and "each cycle of the amplification process generates a plurality of RNA copies from one substrate" (col. 2, lines 49-59). Due to the advantage of generating a plurality of RNA copies, one of ordinary skill would have been motivated minimally to incorporate the features of NASBA taught by Ovyn, into the method of amplification taught by Uematsu, including incorporating the promoter sequence into the primer for generation of additional RNA copies with a reasonable expectation for success. These same benefits would have been obvious if the primer format and universal detection probe taught by Uematsu were

incorporated into the method of NASBA amplification taught by Ovyn to arrive at the claimed invention with a reasonable expectation for success.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Uematsu et al. (Nucleic Acids Research Supplement No. 2, 2002, p. 211-212, public availability date of August 9, 2003, see printout from Pubmed; 'Uematsu 2002' herein) as evidenced by Uematsu et al. (2001, Nucleic Acids Research, vol. 29, no. 16, e84, p. 1-6; 'Uematsu 2001' herein) and further in view of Ovyn et al. (6,101,681; August 2000) as applied to claims 3-7 above and further in view of Rizzo et al. (Molecular and Cellular Probes, 2002, vol. 16, p. 277-283).

Uematsu in view of Ovyn teach the limitations of claims 3-7. Neither Ovyn nor Uematsu teach a probe that is a DNA/RNA hybrid. Rizzo teaches that the probe for detection is labeled at one end with a quencher and that the probe is digested by ribonuclease H (Figure 1, where the probe is a molecular beacon and is labeled at one end with a quencher and at the other end with a fluorophore).

Regarding claim 14, Rizzo teaches an embodiment of claim 1, wherein the probe is a DNA/RNA hybrid (Figure 1, where the probe is comprised of an RNA:DNA hybrid stem).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of expressed gene analysis taught by Ovyn and Uematsu to incorporate an RNA/DNA hybrid probe of the type disclosed by Rizzo. Rizzo states that "here we describe the preparation of an RNA/DNA chimeric molecular beacon, which contains a single-stranded RNA-DNA chimeric oligonucleotide labeled with a 5' fluorescein as fluorophore and a 3'-DABCYL as quencher (Figure 1). The fluorophore of the probe is held in

proximity to the quencher by the stem-loop structure. When the RNA sequence of the RNA:DNA hybrid stem is cleaved, the fluorescence of the fluorophore is manifested." (p. 278, col. 1, 2 paragraph). Furthermore, Rizzo notes that "the chimeric molecular beacon assay for RNAse H is highly sensitive with fluorescent enhancement of up to 40-fold." (p. 282, conclusions). While the chimeric beacon disclosed by Rizzo was not disclosed in the detection of nucleic acids in a format where RNAse H was present, noting the teaching by Rizzo of a molecular beacon with sensitivity to RNAse H activity, it would have been obvious to one of ordinary skill in the art of NASBA amplification, a method in which RNAse H is often included, to incorporate the molecular beacon disclosed by Rizzo into the method of amplification and detection taught by Ovyn with a reasonable expectation for success.

Claims 1-7, 9, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitcombe et al. (Clinical Chemistry, 1998, 44(5), p. 918-923) in view of Ovyn et al. (6,101,681; August 2000) and Uematsu et al. (2001, Nucleic Acids Research, vol. 29, no. 16, e84, p. 1-6; 'Uematsu 2001' herein). Whitcombe teaches a method of amplification and fluorescence detection using a technique that is 'universal' and can allow for single tube genotyping of more than one target (Abstract, Figure 1).

With regard to claim 1, Whitcombe teaches a method for expressed gene analysis comprising: subjecting a gene to be analyzed to nucleic acid amplification using a forward primer specifically hybridizing to the gene to be analyzed, a primer for introduction comprising a first base sequence closer to the 5' end of the primer than a third base sequence comprising a sequence specifically hybridizing to a target gene, the tarqet gene havinq a base sequence, and

comprising a second base sequence closer to the 5' end of the primer than the first base sequence (Figure 1, where the forward primer specifically hybridizes to the gene to be analyzed, see black arrow portion of primer comprising the target-specific base sequence; also the primer of Figure 1 comprises a first and second base sequence in addition to the target specific portion), a probe comprising a base sequence identical or complementary to the first base sequence (Figure 1, where the probe is complementary to a base sequence which is non-specific to the target) and labeled at one end with a fluorophore and at another end with a quencher (Figure 1, where the probe is complementary to a base sequence that is non-specific to the target and where the probe is labeled at one end with a fluorophore and another with a quencher), digesting the probe bound to the first base sequence by the ribonuclease H or exonuclease at the time of the nucleic acid amplification (bottom of Figure 1, where the probe is digested); and wherein two or more target genes are simultaneously detected in a single reaction vessel using two or more types of probes (Figure 2, where more than one probe is used to detect two or more targets in a single tube; see Table 1, where the FAM and TET probes are depicted); and

detecting fluorescence emitted by the released fluorophore, thereby assaying the amount of the product of the nucleic acid amplification (Figure 2, where the amount of fluorescence emitted by the fluorophore is detected to assay the amount of product of nucleic acid amplification),

wherein the gene to be analyzed is prepared by the introduction of the first base sequence beinq nonspecific to the base sequence of the tarqet gene and the second base sequence, into the target gene so that the second base sequence is bound to a position closer to a 5' end of the gene to be analyzed than the first base sequence (Figure 1, where the forward primer specifically hybridizes to the gene to be analyzed, see black arrow portion of primer comprising the third target-specific

base sequence; also the primer of Figure 1 comprises a first and second base sequence in addition to the target specific portion which are nonspecific to the base sequence of the target).

With regard to claim 9, Whitcombe teaches an embodiment of claim 1, wherein the melting temperatures (Tm values) of the two or more types of probes are substantially the same (Figure 2, where more than one probe is used to detect two or more targets in a single tube; see Table 1, where the FAM and TET probes are depicted).

Regarding claim 1, Whitcombe does not teach the inclusion of reverse transcriptase, RNA polymerase, and ribonuclease H and/or exonuclease and also does not teach that the second base sequence comprising a promoter sequence of RNA polymerase, into the target gene so that the second base sequence is bound to a position closer to a 5' end of the gene to be analyzed than the first base sequence.

With regard to claim 1, Ovyn teaches a method for expressed gene analysis, which comprises the steps of: A) subjecting a gene to be analyzed to nucleic acid amplification using 2) a primer for introduction comprising a second base sequence closer to the 5' end of the primer than the first base sequence (col. 4, lines 48-62, where the primer may include a promoter sequence) 4) reverse transcriptase (col. 2, lines 65-66; see also Figure 1, where the reverse transcriptase is AMV-RT), 5) RNA polymerase (col. 2, lines 65-66, where the RNA polymerase is T7 RNA polymerase, see also Figure 1), and 6) ribonuclease H and/or exonuclease (col. 2, lines 65-66, see Figure 1); and

C) detecting fluorescence emitted by the released fluorophore, thereby assaying the amount of the product of the nucleic acid amplification (col. 9, lines 45-55, where detection probes were hybridized to horseradish peroxidase and the amount of HRP conjugated oligonucleotides was

measured to detect target sequence; however as noted at col. 6, lines 30-37, the probe may also be labeled by fluorescent moieties),

wherein the gene to be analyzed is prepared by the introduction of the first base sequence and the second base sequence comprising a promoter sequence of RNA polymerase, which are non-specific to the base sequence of the target gene, into the target gene so that the second base sequence is bound to a position closer to the 5' end of the gene to be analyzed than the first base sequence (see Figure 1 and description recited above).

With regard to claim 2, Ovyn teaches an embodiment of claim 1, wherein the gene to be analyzed is cDNA comprising the first base sequence and the second base sequence introduced therein by the introduction with subjecting mRNA of the target gene to reverse transcription using the primer for introduction which comprises the first base sequence as described for claim 1 above, in step A) 2) (col. 5, lines 46-64, where primer P1 hybridizes to the RNA to prime and initiate 1st strand synthesis and where after second strand synthesis, the complete cDNA includes the T7 promoter site from the P1 primer).

With regard to claims 3 and 4, Ovyn teaches an embodiment of claim 1, wherein the nucleic acid amplification is conducted by sequentially repeating the following steps 1) to 3):

1) transcription of the gene to analyzed into RNA with the aid of RNA polymerase (col. 5, lines 46-67, see also Figure 1);

2) reverse transcription of the RNA using the forward primer and the reverse transcriptase or ribonuclease H to synthesize single-stranded cDNA (see Figure 1); and

3) synthesis of the gene to be analyzed from the single-stranded cDNA using the primer for introduction and DNA polymerase (col. 5, lines 46-67 and Figure 1).

With regard to claim 5, Ovyn teaches an embodiment of claim 1, wherein the nucleic acid amplification is conducted at a substantially single temperature (col. 10, lines 15-25, where isothermal amplification of the target RNA was performed at 41°C).

With regard to claim 6, Ovyn teaches an embodiment of claim 5, wherein the single temperature is between 37°C and 55°C (col. 10, lines 15-25, where isothermal amplification of the target RNA was performed at 41°C and wherein 41°C is between 37°C and 55°C).

With regard to claim 7, Ovyn teaches an embodiment of claim 1, wherein the RNA polymerase is T7 RNA polymerase and the second base sequence comprises the T7 promoter sequence (col. 5, lines 46-64, where primer P1 hybridizes to the RNA to prime and initiate 1st strand synthesis and where after second strand synthesis, the complete cDNA includes the T7 promoter site from the P1 primer; see also Figure 1).

Regarding claim 1, neither Whitcombe nor Ovyn teaches that wherein each of the two or more types of probes comprise several module sequences of 3 or 4 bases, both of the terminal bases of each module sequence are identical to each other and each probe is constituted by rearranging the order of the module sequences having identical terminal bases.

With regard to claim 1, Uematsu teaches that wherein each of the two or more types of probes comprise several module sequences of 3 or 4 bases, both of the terminal bases of each module sequence are identical to each other and each probe is constituted by rearranging the order of the module sequences having identical terminal bases (Abstract, where the modules were 3 or 4 nt in length; Figure 1, where the primers are comprised of modules consitituted of rearranging the order of the module sequences).

With regard to claim 9, Uematsu teaches wherein the melting temperatures (Tm values) of the two or more types of probes are substantially the same (Figure 1, where the melting temperatures are identical; Abstract).

With regard to claim 15, Uematsu 2002 teaches an embodiment of claim 1, wherein the two or more types of probe respectively have fluorophores at one end that emit light at fluorescent wavelengths different from each other (Figure 1, where the probes are labeled with different reporter fluorophores, R1 and R2; see also p. 212, col. 1, where the labels comprise FAM and VIC).

With regard to claim 16, Uematsu 2002 teaches an embodiment of claim 1, wherein a number of module sequences constituting each probe is in a range of 5 to 8 (p. 211; as evidenced by Uematsu 2001, Figure 1, where the modular primers included at least six different modular sequences within each primer).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the primer formulation, including a target-specific component and a target non-specific component specific to the probe sequence taught by Whitcombe into the method of NASBA amplification taught generally by Ovyn to arrive at the claimed invention with a reasonable expectation for success. Whitcombe teaches a method called Three-STAR which is "universal in that it can either use a single probe for the detection of any one target DNA sequence or a single pair of probes for genotyping any bi-allelic polymorphism" and is "particularly useful for the single-tube genotyping of a variety of human DNA polymorphisms" (Abstract). Furthermore, Whitcombe teaches "we have devised a way to make TaqMan generic in as much that just one fluorogenic probe can be universally applied in any PCR reaction" (p.

921, col. 1-2). Furthermore, the inclusion of a third primer portion, comprising an RNA promoter sequence, would have also been an obvious and necessary substitution to the three-part primer described by Whitcombe for the use of the primers in a NASBA amplification format as taught by Ovyn. Regarding the application of this primer format to additional means of amplification, Ovyn teaches a method known as nucleic acid sequence based amplification (NASBA) (col. 2, lines 46-49). Ovyn describes NASBA as "an amplification system that has significant advantages over PCR amplification systems" because it "requires less user participation and fewer manipulations and steps" and "each cycle of the amplification process generates a plurality of RNA copies from one substrate" (col. 2, lines 49-59). Due to the advantage of generating a plurality of RNA copies, one of ordinary skill would have been motivated minimally to incorporate the features of NASBA taught by Ovyn, into the method of amplification taught by Whitcombe, including incorporating the promoter sequence into the primer for generation of additional RNA copies with a reasonable expectation for success.

Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the module shuffling probes of Uematsu 2002 into the method of gene expression analysis taught by Ovyn and Whitcombe to arrive at the claimed invention with a reasonable expectation for success. As taught by Uematsu 2002, the method incorporates “module shuffling sequences as 'universal TaqMan probes'" and the method "can detect different amounts of expressed genes derived from different sources" (Abstract). Uematsu 2002 also teaches that the "sequences of two TaqMan probes consist of module-shuffling sequences. Their sequences are quite different, but their thermodynamic properties are almost the same” and also notes that the probes “are labeled with different reporter fluorophores

at the 5' end and labeled with quencher and Tm enhancer at the 3' end" (p. 211, col. 1). Finally, Uematsu 2002 notes "the MPT method does not require internal standards and MTPs are applicable to any genes as 'universal TaqMan probes'" (p. 212, col. 2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have incorporated the module shuffling probes of Uematsu 2002 into the method of gene expression analysis taught by Ovyn and Whitcombe to achieve universal detection using probes with different sequences with the same thermodynamic properties with a reasonable expectation for success.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Whitcombe et al. (Clinical Chemistry, 1998, 44(5), p. 918-923) in view of Ovyn et al. (6,101,681; August 2000) and Uematsu et al. (2001, Nucleic Acids Research, vol. 29, no. 16, e84, p. 1-6; 'Uematsu 2001' herein) as applied to claims 1-7, 9, 15 and 16 above and further in view of Rizzo et al. (Molecular and Cellular Probes, 2002, vol. 16, p. 277-283). Whitcombe teaches a method of amplification and fluorescence detection using a technique that is 'universal' and can allow for single tube genotyping of more than one target (Abstract, Figure 1).

Whitcombe in view of Ovyn and Uematsu teach the limitations of claims 1-7 and 9. Neither Whitcombe, Ovyn or Uematsu teach a probe that is a DNA/RNA hybrid. Rizzo teaches that the probe for detection is labeled at one end with a quencher and that the probe is digested by ribonuclease H (Figure 1, where the probe is a molecular beacon and is labeled at one end with a quencher and at the other end with a fluorophore).

Regarding claim 14, Rizzo teaches an embodiment of claim 1, wherein at least one of the two or more types of probes is a DNA/RNA hybrid (Figure 1, where the probe is comprised of an RNA:DNA hybrid stem).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of expressed gene analysis taught by Ovyn to incorporate an RNA/DNA hybrid probe of the type disclosed by Rizzo. Rizzo states that "here we describe the preparation of an RNA/DNA chimeric molecular beacon, which contains a single-stranded RNA-DNA chimeric oligonucleotide labeled with a 5' fluorescein as fluorophore and a 3'-DABCYL as quencher (Figure 1). The fluorophore of the probe is held in proximity to the quencher by the stem-loop structure. When the RNA sequence of the RNA:DNA hybrid stem is cleaved, the fluorescence of the fluorophore is manifested." (p. 278, col. 1, 2 paragraph). Furthermore, Rizzo notes that "the chimeric molecular beacon assay for RNAse H is highly sensitive with fluorescent enhancement of up to 40-fold." (p. 282, conclusions). While the chimeric beacon disclosed by Rizzo was not disclosed in the detection of nucleic acids in a format where RNAse H was present, noting the teaching by Rizzo of a molecular beacon with sensitivity to RNAse H activity, it would have been obvious to one of ordinary skill in the art of NASBA amplification, a method in which RNAse H is often included, to incorporate the molecular beacon disclosed by Rizzo into the method of amplification and detection taught by Ovyn with a reasonable expectation for success.

Claims 1-7, 9, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitcombe et al. (Clinical Chemistry, 1998, 44(5), p. 918-923) in view of Leone et al. (1998,

Nucleic Acids Research, vol. 26, no. 9, p. 2150-2155) as evidenced by Leone et al. (1997, J. Virol. Methods, 66, 19-27) and in view of Uematsu et al. (2001, Nucleic Acids Research, vol. 29, no. 16, e84, p. 1-6; 'Uematsu 2001' herein). Whitcombe teaches a method of amplification and fluorescence detection using a technique that is 'universal' and can allow for single tube genotyping of more than one target (Abstract, Figure 1).

With regard to claim 1, Whitcombe teaches a method for expressed gene analysis comprising: subjecting a gene to be analyzed to nucleic acid amplification using a forward primer specifically hybridizing to the gene to be analyzed, a primer for introduction comprising a first base sequence closer to the 5' end of the primer than a third base sequence comprising a sequence specifically hybridizing to a target gene, the tarqet gene havinq a base sequence, and comprising a second base sequence closer to the 5' end of the primer than the first base sequence (Figure 1, where the forward primer specifically hybridizes to the gene to be analyzed, see black arrow portion of primer comprising the target-specific base sequence; also the primer of Figure 1 comprises a first and second base sequence in addition to the target specific portion), a probe comprising a base sequence identical or complementary to the first base sequence (Figure 1, where the probe is complementary to a base sequence which is non-specific to the target) and labeled at one end with a fluorophore and at another end with a quencher (Figure 1, where the probe is complementary to a base sequence that is non-specific to the target and where the probe is labeled at one end with a fluorophore and another with a quencher), digesting the probe bound to the first base sequence by the ribonuclease H or exonuclease at the time of the nucleic acid amplification (bottom of Figure 1, where the probe is digested); and

wherein two or more target genes are simultaneously detected in a single reaction vessel using

two or more types of probes (Figure 2, where more than one probe is used to detect two or more targets in a single tube; see Table 1, where the FAM and TET probes are depicted);
detecting fluorescence emitted by the released fluorophore, thereby assaying the amount of the product of the nucleic acid amplification (Figure 2, where the amount of fluorescence emitted by the fluorophore is detected to assay the amount of product of nucleic acid amplification), wherein the gene to be analyzed is prepared by the introduction of the first base sequence beinq nonspecific to the base sequence of the tarqet gene and the second base sequence, into the target gene so that the second base sequence is bound to a position closer to a 5' end of the gene to be analyzed than the first base sequence (Figure 1, where the forward primer specifically hybridizes to the gene to be analyzed, see black arrow portion of primer comprising the third target-specific base sequence; also the primer of Figure 1 comprises a first and second base sequence in addition to the target specific portion which are nonspecific to the base sequence of the target).

With regard to claim 9, Whitcombe teaches an embodiment of claim 8, wherein the melting temperatures (Tm values) of the two or more types of probes are substantially the same (Figure 2, where more than one probe is used to detect two or more targets in a single tube; see Table 1, where the FAM and TET probes are depicted).

Regarding claim 1, Whitcombe does not teach that the primer for introduction comprises a second base sequence comprising a promoter sequence of RNA polymerase, which is non-specific to the base sequence of the target gene. Whitcombe also does not teach that the amplification of the gene is accomplished using reverse transcriptase, RNA polymerase and ribonuclease H and/or exonuclease. Leone discloses the use of molecular beacon probes in the detection of nucleic acids amplified by the NASBA technique (Abstract).

With regard to claim 1, Leone teaches a method for expressed gene analysis, which comprises the steps of: A) subjecting a gene to be analyzed to nucleic acid amplification using 1) a forward primer specifically hybridizing to the gene to be analyzed (p. 2151, col. 1, 'selection of amplification primers and probe' heading, where PD415 or PD416 are antisense primers and PD417 is a sense primer, which were designed to amplify the coat protein open reading frame), 2) a primer for introduction comprising a second base sequence closer to the 5' end of the primer than the first base sequence (p. 2154, Figure 6, legend, where it is noted that the amplicon formed by PD415-PD417 or PD416-PD417 contain a binding site for the T7 RNA polymerase, in addition to complementarity to the target sequence, as described in more detail in Leone et al. 1997, J. Virol. Methods, 66, 19-27, see Table 1, where the sequences of PD415-PD417 are given and also the '*2.2 Selection of amplification primers and detection probe*' heading, where "the antisense ones consisted of a 3' terminal target specific sequence and a 5' terminal T7 promoter sequence"), 3) a probe comprising a base sequence identical or complementary to the first base sequence and labeled at one end with a fluorophore (p. 2151, col. 1, 'synthesis of the molecular beacons' heading, where a molecular beacon sw75-F1 was designed to bind to nucleotides within the coat protein ORF of PLRV, with DABCYL at the 3' end and fluoroscein at the 5' end), 4) reverse transcriptase (p. 2151, 'NASBA' heading, where the reverse transcriptase was included as part of the enzyme mix, which included 6.4 U AMV-reverse transcriptase), 5) RNA polymerase (p. 2151, 'NASBA' heading, where the RNA polymerase is T7 and 32 U are included in the enzyme mix), and 6) ribonuclease H and/or exonuclease (p. 2151, 'NASBA' heading, where 0.08 U RNase H is included in the enzyme mix); and

C) detecting fluorescence emitted by the released fluorophore, thereby assaying the amount of the product of the nucleic acid amplification (p. 2151, col. 2 'post-NASBA analysis' and 'Real-time monitoring of NASBA reactions and thermal denaturation profiles' heading, see also Figure 2), wherein the gene to be analyzed is prepared by the introduction of the first base sequence and the second base sequence comprising a promoter sequence of RNA polymerase, which are non-specific to the base sequence of the target gene, into the target gene so that the second base sequence is bound to a position closer to the 5' end of the gene to be analyzed than the first base sequence.

With regard to claim 2, Leone teaches an embodiment of claim 1, wherein the gene to be analyzed is cDNA comprising the first base sequence and the second base sequence introduced therein by the introduction with subjecting mRNA of the target gene to reverse transcription using a primer for introduction which comprises the first base sequence as described for claim 1 above, in step A) 2) (see description above for Step A) 2), also p. 2150, col. 1, where the process of NASBA is described in more detail, where the reaction is based on the concurrent activity of AMV-RT, RNase H and T7 polymerase).

With regard to claims 3 and 4, Leone teaches an embodiment of claim 1, wherein the nucleic acid amplification is conducted by sequentially repeating the following steps 1) to 3):
1) transcription of the gene to analyzed into RNA with the aid of RNA polymerase;
2) reverse transcription of the RNA using the forward primer and the reverse transcriptase or ribonuclease H to synthesize single-stranded cDNA; and
3) synthesis of the gene to be analyzed from the single-stranded cDNA using the primer for introduction and DNA polymerase (p. 2150, col. 1, where the process of NASBA is described in

more detail, where the reaction is based on the concurrent activity of AMV-RT, RNase H and T7 polymerase in repetition and where the activity of these enzymes would include each of the preceeding steps recited, including transcription with an RNA polymerase, reverse transcription, and synthesis of the gene using DNA polymerase).

With regard to claim 5, Leone teaches an embodiment of claim 1, wherein the nucleic acid amplification is conducted at a substantially single temperature (p. 2151, 'NASBA' heading, where besides an incubation at 65°C prior to introduction of the enzyme mix, the reaction occurred at 41°C).

With regard to claim 6, Leone teaches an embodiment of claim 5, wherein the single temperature is between 37°C and 55°C (p. 2151, 'NASBA' heading, where besides an incubation at 65°C prior to introduction of the enzyme mix, the reaction occurred at 41°C).

With regard to claim 7, Leone teaches an embodiment of claim 1, wherein the RNA polymerase is T7 RNA polymerase and the second base sequence comprises the T7 promoter sequence (p. 2154, Figure 6, legend, where it is noted that the amplicon formed by PD415-PD417 or PD416-PD417 contain a binding site for the T7 RNA polymerase, in addition to complementarity to the target sequence, as described in more detail in Leone et al. 1997, J. Virol. Methods, 66, 19-27, see Table 1, where the sequences of PD415-PD417 are given and also the '*2.2 Selection of amplification primers and detection probe*' heading, where "the antisense ones consisted of a 3' terminal target specific sequence and a 5' terminal T7 promoter sequence").

Regarding claim 1, neither Whitcombe nor Leone teaches that wherein each of the two or more types of probes comprise several module sequences of 3 or 4 bases, both of the terminal

bases of each module sequence are identical to each other and each probe is constituted by rearranging the order of the module sequences having identical terminal bases.

With regard to claim 1, Uematsu teaches that wherein each of the two or more types of probes comprise several module sequences of 3 or 4 bases, both of the terminal bases of each module sequence are identical to each other and each probe is constituted by rearranging the order of the module sequences having identical terminal bases (Abstract, where the modules were 3 or 4 nt in length; Figure 1, where the primers are comprised of modules consitituted of rearranging the order of the module sequences).

With regard to claim 9, Uematsu teaches wherein the melting temperatures (Tm values) of the two or more types of probes are substantially the same (Figure 1, where the melting temperatures are identical; Abstract).

With regard to claim 15, Uematsu 2002 teaches an embodiment of claim 1, wherein the two or more types of probe respectively have fluorophores at one end that emit light at fluorescent wavelengths different from each other (Figure 1, where the probes are labeled with different reporter fluorophores, R1 and R2; see also p. 212, col. 1, where the labels comprise FAM and VIC).

With regard to claim 16, Uematsu 2002 teaches an embodiment of claim 1, wherein a number of module sequences constituting each probe is in a range of 5 to 8 (p. 211; as evidenced by Uematsu 2001, Figure 1, where the modular primers included at least six different modular sequences within each primer).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to apply the primer formulation, including a target-specific component and a

target non-specific component specific to the probe sequence taught by Whitcombe into the method of NASBA amplification taught generally by Leone to arrive at the claimed invention with a reasonable expectation for success. Whitcombe teaches a method called Three-STAR which is "universal in that it can either use a single probe for the detection of any one target DNA sequence or a single pair of probes for genotyping any bi-allelic polymorphism" and is "particularly useful for the single-tube genotyping of a variety of human DNA polymorphisms" (Abstract). Furthermore, Whitcombe teaches "we have devised a way to make TaqMan generic in as much that just one fluorogenic probe can be universally applied in any PCR reaction" (p. 921, col. 1-2). Furthermore, the inclusion of a third primer portion, comprising an RNA promoter sequence, would have also been an obvious and necessary substitution to the three-part primer described by Whitcombe for the use of the primers in a NASBA amplification format as taught by Leone. Regarding the application of this primer format to additional means of amplification, Leone teaches a method known as nucleic acid sequence based amplification (NASBA) (p. 2150, Abstract, col. 1). Leone states "with respect to other amplification systems such as the PCR technique, the ability of NASBA to homogeneously and isothermally amplify RNA analytes (e.g., viral genomic RNA, mRNA or rRNA) extends its application range from viral diagnostics to the indication of biological activities such as gene expression and cell viability" (p. 2150, col. 1). Leone also states that NASBA "results in exponential amplification of RNA and DNA products within 90 min, producing as the major amplification product antisense, single-stranded RNA" (p. 2150, col. 1). Due to the advantage of generating a plurality of RNA copies, one of ordinary skill would have been motivated minimally to incorporate the features of NASBA taught by Leone, into the method of amplification taught by Whitcombe,

including incorporating the promoter sequence into the primer for generation of additional RNA copies with a reasonable expectation for success.

Finally, the commonality of detection, as taught by Leone, describing "the coupling of RNA amplification by NASBA with amplicon detection by molecular beacons technology to produce a truly homogeneous RNA assay, called AmpliDet RNA" and report "how molecular beacons improve NASBA, enabling a one-tube assay suitable for high-throughput applications without compromising specificity and sensitivity" (p. 2151, col. 1). Therefore, one of ordinary skill would have been motivated to incorporate the promoter sequence taught by Leone into the primer formation taught by Whitcombe to achieve one-tube, high throughput assay of nucleic acid targets with a reasonable expectation for success.

Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the module shuffling probes of Uematsu 2002 into the method of gene expression analysis taught by Whitcombe and Leone to arrive at the claimed invention with a reasonable expectation for success. As taught by Uematsu 2002, the method incorporates "module shuffling sequences as 'universal TaqMan probes'" and the method "can detect different amounts of expressed genes derived from different sources" (Abstract). Uematsu 2002 also teaches that the "sequences of two TaqMan probes consist of module-shuffling sequences. Their sequences are quite different, but their thermodynamic properties are almost the same" and also notes that the probes "are labeled with different reporter fluorophores at the 5' end and labeled with quencher and Tm enhancer at the 3' end" (p. 211, col. 1). Finally, Uematsu 2002 notes "the MPT method does not require internal standards and MTPs are applicable to any genes as 'universal TaqMan probes'" (p. 212, col. 2). Therefore, one of

ordinary skill in the art at the time the invention was made would have been motivated to have incorporated the module shuffling probes of Uematsu 2002 into the method of gene expression analysis taught by Whitcombe and Leone to achieve universal detection using probes with different sequences with the same thermodynamic properties with a reasonable expectation for success.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Whitcombe et al. (Clinical Chemistry, 1998, 44(5), p. 918-923) in view of Leone et al. (1998, Nucleic Acids Research, vol. 26, no. 9, p. 2150-2155) as evidenced by Leone et al. (1997, J. Virol. Methods, 66, 19-27) and further in view of Uematsu et al. (2001, Nucleic Acids Research, vol. 29, no. 16, e84, p. 1-6; 'Uematsu 2001' herein) as applied to claims 1-7 and 9 above and further in view of Rizzo et al. (Molecular and Cellular Probes, 2002, vol. 16, p. 277-283). Whitcombe teaches a method of amplification and fluorescence detection using a technique that is 'universal' and can allow for single tube genotyping of more than one target (Abstract, Figure 1).

Whitcombe in view of Leone and Uematsu teach the limitations of claims 1-7 and 9. Whitcombe nor Leone or Uematsu teach a probe that is a DNA/RNA hybrid. Rizzo teaches that the probe for detection is labeled at one end with a quencher and that the probe is digested by ribonuclease H (Figure 1, where the probe is a molecular beacon and is labeled at one end with a quencher and at the other end with a fluorophore).

Regarding claim 14, Rizzo teaches an embodiment of claim 1, wherein at least one of the two or more types of probes is a DNA/RNA hybrid (Figure 1, where the probe is comprised of an RNA:DNA hybrid stem).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of expressed gene analysis taught by Leone to incorporate an RNA/DNA hybrid probe of the type disclosed by Rizzo. Rizzo states that "here we describe the preparation of an RNA/DNA chimeric molecular beacon, which contains a single-stranded RNA-DNA chimeric oligonucleotide labeled with a 5' fluorescein as fluorophore and a 3'-DABCYL as quencher (Figure 1). The fluorophore of the probe is held in proximity to the quencher by the stem-loop structure. When the RNA sequence of the RNA:DNA hybrid stem is cleaved, the fluorescence of the fluorophore is manifested." (p. 278, col. 1, 2 paragraph). Furthermore, Rizzo notes that "the chimeric molecular beacon assay for RNAse H is highly sensitive with fluorescent enhancement of up to 40-fold." (p. 282, conclusions). While the chimeric beacon disclosed by Rizzo was not disclosed in the detection of nucleic acids in a format where RNAse H was present, noting the teaching by Rizzo of a molecular beacon with sensitivity to RNAse H activity, it would have been obvious to one of ordinary skill in the art of NASBA amplification, a method in which RNAse H is often included, to incorporate the molecular beacon disclosed by Rizzo into the method of amplification and detection taught by Leone with a reasonable expectation for success.

Response to Arguments

Applicant's arguments with respect to claims 1-7, 9, 14 and 16 have been considered but are moot in view of the new ground(s) of rejection. While Applicant addresses the Ovyn, Whitcombe, Leone and Rizzo references still applied in the current action, these arguments are based primarily on how these references relate to the newly added limitations. As new grounds

of rejection have been made in view of Uematsu 2001, these arguments are moot. However, insofar as the arguments apply over the rejections as previously submitted, the arguments will be addressed.

Regarding Whitcombe, Applicant traverses the rejection and argues that Whitcombe "discloses a probe non-specific to a target gene, and genotyping of 2 or more target genes in a single tube... in a single sample" and states "in contrast, two or more different target genes, e.g., derived from different samples, are detected in the present invention, using two or more probes having substantially the same Tm value" (p. 12 of remarks).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., two or more target genes derived from different samples) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, regarding the melting temperature of the probes, Applicant asserts "the FAM probe and TET probe in Fig 2 of Whitcombe et al. are shown below and respectively have melting temperatures of 65 and 72oC" and conclude that they have different Tm values". It is noted in response that the claim merely requires that the melting temperatures are substantially the same. It is interpreted that this range of temperatures are substantially the same, meeting this limitation of the claim. The additional limitations directed to the module shuffling have been addressed by the inclusion of Uematsu 2001 and 2002. The rejections are maintained.

Related Prior Art

1. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Koteler et al. (PNAS, 1993, vol. 90, p. 4241-4245) teaches modular primes assembled from pentamers and hexamers (Abstract).

2. Yu et al. (WO03/038119; published May 2003) disclose a method of amplification of foot and mouth disease virus (FDMV) using NASBA with detection using chemiluminescence. Rossi et al. (US Patent 5,783,391; July 1998) disclose a method of amplification via cylic amplification using reverse transcriptase and T7 RNA polymerase, however the ribonuclease is RNase A. de Barr et al. (2001, Journal of Clinical Microbiology, p. 1895-1902) disclose a method for isothermal amplification to identify multiple subtypes of HIV-1 using NASBA amplification and molecular beacons.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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